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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/501,207 | 09/22/2005 | John Arthur Hohneker | ONC/4-32312A | 3237 |

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

| EXAMINER | |
|---|---|
| LEWIS, PATRICK T | |

| ART UNIT | PAPER NUMBER |
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| 1623 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/501,207 | HOHNEKER ET AL. | |
| | Examiner | Art Unit | |
| | Patrick T. Lewis | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Applicant's Response Dated July 22, 2008*

1. Claims 1-9 and 14 are pending. An action on the merits of claims 1-9 and 14 is contained herein below.

2. The rejection of claims 10-12 under 35 U.S.C. 101 and 35 U.S.C. 112, second paragraph, has been rendered moot in view of applicant's amendment dated July 22, 2008.

3. The rejection of claims 1-9 under 35 U.S.C. 103(a) as being unpatentable over Altmann et al. US 6,387,927 (Altmann) and Trimble et al. Expert Opin. Pharmaother. (2001), Vol. 2, pages 1299-1306 (Trimble) is maintained for the reasons of record set forth in the Office Action dated January 24, 2008.

4. The rejection of claims 10-13 under 35 U.S.C. 103(a) as being unpatentable over Altmann et al. US 6,387,927 (Altmann) and Trimble et al. Expert Opin. Pharmaother. (2001), Vol. 2, pages 1299-1306 (Trimble) has been rendered moot in view of applicant's amendment dated July 22, 2008.

### *Rejections of Record Set Forth in the Office Action Dated January 24, 2008*

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altmann et al. US 6,387,927 (Altmann) and Trimble et al. Expert Opin. Pharmaother. (2001), Vol. 2, pages 1299-1306 (Trimble).

Claims 1-7 and 9 are drawn to a combination comprising (a) an antineoplastic antimetabolite and(b) an epothiolone derivative of formula (I). Claim 8 is drawn to a method to treating a proliferative disease comprising administering to an animal a combination according to claim 1.

Altmann teaches that Epothilones A and B represent a new class of microtubule-stabilizing cytotoxic agents (column 1, lines 19-43). These compounds have advantages over TAXOL, a branded product already introduced for the treatment of tumors, that has the same mechanism of action but has however a series of disadvantages, such as very poor water solubility, making the preparation of pharmaceutical formulations very difficult (such formulations are normally characterized by the toxic side effects of the carrier materials), and inefficacy on a series of tumors. Altmann further teaches epothilone derivatives of formula (I) which are pharmacologically highly effective (column 2, line 23 to column 3, line 19). Altmann teaches modifications to the epothilone core embraced by instantly claimed variables A, R, Z and R'. Altmann further teaches that the epothilone derivatives can be administered alone or in combination with one or more other therapeutic agents (column 8, lines 1-27).

Altmann differs from the instantly claimed invention in that Altmann does not explicitly teach the instant derivatives of formula (I). Altmann also does not explicitly

teach the use of specifically claimed antineoplastic antimetabolites; however, these differences would have been obvious to one of ordinary skill in the art at the time of the invention.

It would have been obvious to the skilled artisan to modify Epothiloone A or B with the instantly claimed moieties of A, R, Z and R'. Altmann teaches that the instantly claimed modifications to the chemical core may be made while conserving pharmacological activity. The skilled artisan would have been motivated to make the instantly claimed derivatives because of their expected pharmacological activity. The use of conventional antineoplastic antimetabolites such as 5-fluorouracil, tegafur, gemcitabine and capecitabine (see Trimble, pages 1300-1304) in the combination taught by Altmann is prima facie obvious.

7. Applicant's arguments filed July 22, 2008 have been fully considered but they are not persuasive. Applicant argues that although Trimble et al. discloses antimetabolites and indicates that an epothilone derivative is under investigation, the reference fails to provide any motivation for the artisan to combine an antimetabolite and an epothilone together.

The examiner respectfully disagrees. Use of materials in combination, each of which is known to function for intended purpose, is generally held to be prima facie obvious as the idea of combining them flows logically from their having been individually taught in the prior art. In the instant case, Altmann teaches epothilone derivatives of formula (I) which useful for the treatment of tumors. The use of conventional antineoplastic antimetabolites such as 5-fluorouracil, tegafur, gemcitabine and

capecitabine for treating tumors was well-known at the time of the instant invention. Thus, claims that require no more than the administration of two conventional anti-tumor compositions together in order to treat tumors in a patient set forth prima facie obvious subject matter.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Altmann et al. US 6,387,927 (Altmann) and Trimble et al. Expert Opin. Pharmaother. (2001), Vol. 2, pages 1299-1306 (Trimble).

Claim 14 is drawn to a method to treating a proliferative disease comprising administering to a patient a combination according to claim 1.

Altmann teaches that Epothilones A and B represent a new class of microtubule-stabilizing cytotoxic agents (column 1, lines 19-43). These compounds have advantages over TAXOL, a branded product already introduced for the treatment of tumors, that has the same mechanism of action but has however a series of disadvantages, such as very poor water solubility, making the preparation of pharmaceutical formulations very difficult (such formulations are normally characterized by the toxic side effects of the carrier materials), and inefficacy on a series of tumors. Altmann further teaches epothilone derivatives of formula (I) which are pharmacologically highly effective (column 2, line 23 to column 3, line 19). Altmann teaches modifications to the epothilone core embraced by instantly claimed variables A, R, Z and R'. Altmann further teaches that the epothilone derivatives can be administered alone or in combination with one or more other therapeutic agents (column 8, lines 1-27).

Altmann differs from the instantly claimed invention in that Altmann does not explicitly teach the instant derivatives of formula (I). Altmann also does not explicitly

teach the use of specifically claimed antineoplastic antimetabolites; however, these differences would have been obvious to one of ordinary skill in the art at the time of the invention.

It would have been obvious to the skilled artisan to modify Epothiloone A or B with the instantly claimed moieties of A, R, Z and R'. Altmann teaches that the instantly claimed modifications to the chemical core may be made while conserving pharmacological activity. The skilled artisan would have been motivated to make the instantly claimed derivatives because of their expected pharmacological activity. The use of conventional antineoplastic antimetabolites such as 5-fluorouracil, tegafur, gemcitabine and capecitabine (see Trimble, pages 1300-1304) in the combination taught by Altmann is prima facie obvious.

***Conclusion***

12. Claims 1-9 and 14 are pending. Claims 1-9 and 14 are rejected. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Contacts***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dr. Patrick T. Lewis/
Primary Examiner, Art Unit 1623

ptl